Active syphilis in HIV infection: a multicentre retrospective survey

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Objective: To study syphilis in HIV infection focusing on immunocompromised patients with an atypical or aggressive clinical course of syphilis, inappropriate serological reactions or an unreliable response to therapy.
Study design: A multicentre retrospective chart review using a standardised questionnaire for all patients with active syphilis.
Settings: Thirteen dermatological and medical centres throughout Germany, all members of the German AIDS Study Group (GASG).
Patients: Clinical data of 11368 HIV infected patients have been analysed for cases of active syphilis requiring treatment. Asymptotic patients with reactive serological parameters indicating latent syphilis without a need for treatment were excluded.
Results: Active syphilis was reported in 151 of 11 368 HIV infected patients (1·33%, range per centre 0·3%–5·1%). Most of the 151 syphilis patients were male (93%) and belonged to the homosexual or bisexual exposure category for HIV infection (79%); another 6% were iv drug users. Among the 151 syphilis patients primary syphilis was diagnosed in 17·2%, maculopapular secondary syphilis in 29·1%, ulcerating secondary syphilis in 7·3%, neurosyphilis in 16·6% and latent seropositive syphilis without clinical symptoms but serological abnormalities indicating active syphilis in 25·2%.

A history of prior treatments for syphilis was reported in 50%. At the time of syphilis diagnosis 26·5% of the patients were in CDC stage II, 33·8% in stage III and 24·5% in stage IV of HIV disease (CDC classification 1987). CD4 cell count was lowest in those with ulcerating secondary syphilis (mean 307, SD 140/μl) and neurosyphilis (351, SD 235/μl). The highest CD4 count was found in patients with early primary and early secondary syphilis (444, SD 163/μl and 470, SD 355/μl). Inappropriate serological response to syphilis infection was found in 81 of 151 patients (54%). Remarkable findings were false negative VDRL titres (11 patients with non primary syphilis), false negative TPHA (1) or 19S-IgM-FTA-ABS-tests (16), and strongly reactive VDRL (⩾ 512, 8) or TPHA titres (⩾ 10 240, 47). Treatment failures were reported in at least 6 of 151 cases (4%).
Conclusions: Atypical clinical and serological courses of syphilis were observed in HIV infected patients. Ulcerating secondary syphilis with general symptoms ("malignant syphilis") was 60 times more frequent than in historic syphilis series. Neurosyphilis was found in one sixth of those with active syphilis. Therefore lumbar puncture should be considered a routine in coinfections with HIV and syphilis. Treatment efficacy should be monitored carefully.
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Introduction

In Western Europe and North America there is a strong epidemiological association between HIV-infection and syphilis. Both diseases are generally transmitted by homosexual or heterosexual intercourse. In consequence gay or bisexual men with many sex-partners and intravenous drug users of both genders have a high risk of being infected.

As shown by Quinn[1] and other authors[2–3] HIV infection is found in 0·9 to 5·3% of all patients attending clinics for sexual transmitted diseases. Vice versa there is a high serological evidence for syphilis in 26 to 58% of all German HIV patients, as pointed out by three different subgroups of the German AIDS Study Group (GASG).[4–6]

In HIV infected patients it has been reported that syphilis shows atypical clinical and serological courses,[7–8] unreliable response to therapy[8–10] and premature development of neurosyphilis.[10 11] Despite the large number of case reports dealing with these abnormalities, little is known about the natural history and the incidence of such cases in patients with concomitant HIV infection.

Supported by the German Ministry of Health 13 dermatological and medical centres (all members of the German AIDS Study Group analysed cases of active syphilis in HIV infection.

Methods

In a retrospective multicentre chart review 11 368 HIV infected patients were studied for any clinical or serological evidence of active syphilis. These patients were seen at 13 different centres of dermatology or internal medicine throughout Germany. Inclusion criteria for evaluation were serologically confirmed HIV infection, apparent syphilis lesions (such

as primary ulcers, syphilides, neurosyphilis) and furthermore patients with a serology indicating a need for treatment (reactive TPHA titres with high VDRL titres or specific IgM titres). Patients with a history of syphilis treated sufficiently in the past and patients without any clinical or serological signs of active or reactivated syphilis were excluded. Because different serological syphilis tests were used without having a reference laboratory, it was the individual investigator's decision whether syphilis required treatment or was residual. Primary syphilis was diagnosed on the basis of a positive dark-field examination. Serological tests mostly used in this study were VDRL (Venereal Disease Research Laboratory), TPHA (*Treponema Pallida* Hemagglutination Assay), 19S-IgM-FTA-ABS (19S-IgM Fluorescence Treponemal Antibody Absorption test) and SPHA (Solid-Phase Hemagglutination Assay). Other cardiolipin tests like the RPR (Rapid Plasma Reagin test) which had been performed in a few cases (20/151) were not evaluated. The results of these tests were classified in four categories: not reactive (VDRL negative, TPHA negative), weak reactive (VDRL $\leqslant 8$, TPHA $\leqslant 160$), reactive (VDRL 16–256, TPHA 320–5120) and strongly reactive (VDRL $\geqslant 512$, TPHA $\geqslant 10\,240$). 19S-IgM-FTA-ABS- and SPHA-tests were classified as reactive or not reactive without quantification. Secondary syphilis was diagnosed by clinical symptoms, serology and in a few cases by a characteristic histology. We distinguished between maculopapular syphilides and ulcerating syphilides which were almost regularly accompanied by general symptoms. Diagnostic criteria for tertiary syphilis were histologically confirmed tuberoserpiginous or gummatous lesions. Neurosyphilis was defined by clinical symptoms, seropositivity for syphilis and a reactive VDRL and/or TPHA titre in the cerebrospinal fluid (CSF), positive protein and lymphocytic pleocytosis (WBC > 5 cells/μl). Five patients with clinical symptoms of neurosyphilis, but lacking or questionable CSF findings, had been treated as neurosyphilis for safety reasons. Since they did not fulfill all requirements for neurosyphilis, they were excluded from further evaluation in the neurosyphilis group.

Data concerning age, gender, exposure category for HIV infection, history of syphilis, clinical symptoms of syphilis, therapeutic regimen and response to therapy were collected by using a standardised questionnaire for each individual patient with active syphilis. Furthermore the stage of HIV disease (CDC 1987[12]), the absolute CD4 cell count/μl, the actual and if available the former syphilis serology parameters as well as CSF parameters were evaluated. Treatment regimens for syphilis had not been standardised in this retrospective study. Treatment failures were defined as a lack of clinical response and/or serological response (that is, at least a fourfold drop of titres). Statistical analysis was performed at the scientific secretariat of GASG, Munich. Due to the retrospective nature of the investigation, descriptional statistics were applied.

Results

Age, gender, risk groups In this study 151 of 11 368 HIV positive patients (1·33%) were diagnosed with clinical or serological active syphilis requiring treatment. The mean age of these syphilis patients was 37·2, SD 10·4 years. Most of the patients (141 of 151) were male (93·4%), and 10 were female (6·6%). Three quarters (78·8%) were homosexual or bisexual men and 6% were iv drug users. HIV infection was acquired heterosexually in 1·3%, 1·3% by blood products and 2% by sexual contacts in areas endemic for HIV infection. No information about risk factors was available in 9·9%. Concerning age, gender and mode of HIV transmission the 151 patients with syphilis showed no relevant difference to the typical pattern in German AIDS patients.[13]

History of Syphilis Seventy six of 151 patients (50·3%) had a prior history of at least one syphilis episode (including 11 patients with two, 2 patients with three and 1 patient with four episodes). The mean time since the last syphilis episode was 6·72, SD 6·02 years. In the group of patients with primary ulcers this period was remarkably longer (10·86, SD 6·34 years) than in patients with secondary or tertiary syphilis. Forty nine of 151 patients (32·5%) had no history of syphilis and from 26 of 151 (17·2%) no detailed information was obtained.

Stage of HIV disease At the time syphilis was diagnosed 1 out of 151 (0·7%) patients was in stage CDC I, 40 (26·5%) were in CDC II, 51 (33·8%) in CDC III and 37 (24·5%) in CDC IV. The CDC stage was not reported in 22 patients (14·5%).

Manifestation of active syphilis Primary syphilis (primary ulcer) was diagnosed in 26 of 151 (17·2%) patients, secondary syphilis with typical maculopapular syphilides in 44 (29·1%), ulcerating secondary syphilis with general symptoms in 11 (7·3%), gummata (1 testicular, 1 subcutaneous gumma) in 2 (1·3%), neurosyphilis in 25 (16·6%) and latent syphilis with serological abnormalities indicating a need for treatment in 38 (25·2%). Five patients (3·3%) were not classified in these categories.

Syphilis manifestation in the different CDC stages (table 1). In general, primary syphilis or maculopapular secondary syphilis was the main manifestation in patients with HIV disease stage CDC II or III. Furthermore, some cases of neurosyphilis or latent syphilis with signs of serological activity were diagnosed.

As shown in table 1 early syphilis with primary ulcers or maculopapular exanthema was more frequent in early stages of HIV disease, whereas ulcerating secondary syphilis and neurosyphilis were predominant in advanced stages of HIV disease (CDC III, IV) with distinct immunodeficiency (low CD4 cell counts).

Mean CD4 cell count at the time of syphilis diagnosis (table 2) The mean absolute CD4

Table 1 Clinical manifestations of syphilis and stage of HIV disease in 151 HIV infected patients

	Primary syphilis	*Secondary syphilis, syphilides*	*Secondary syphilis, ulcerating*	*Neuro-syphilis*	*Latent syphilis seropositive*	*Others*	*Patients n*	*%*
CDC I	—	1	—	—	—	—	1	(0·70)
CDC II	10	15	1	7	6	1	40	(26·5)
CDC III	9	15	6	3	15	3	51	(33·8)
CDC IV	1	7	2	12	12	3	37	(24·5)
CDC unknown	6	6	2	3	5	—	22	(14·5)
Patients n	26	44	11	25	38	7	151	
(%)	(17·2)	(29·1)	(7·3)	(16·6)	(25·2)	(4·6)		(100)

Table 2 CD4 cell count in HIV patients at the time of syphilis diagnosis

	Primary syphilis total: 26 patients	*Secondary syphilis, syphilides 44 patients*	*Secondary syphilis, ulcerating 11 patients*	*Neuro-syphilis 25 patients*	*Latent syphilis, seropositive 38 patients*	*Others 7 patients*
$CD4^+$ T-cells (mean/μl)	444	470	307	351	359	257
SD	163	355	140	235	279	209
Patients with valid CD4 counts	22	32	9	20	26	7

cell count was relatively high in patients with primary syphilis (22 patients, CD4 = 444, SD 163/μl) and maculopapular syphilides (32 patients, CD4 = 470, SD 355/μl) whereas patients with ulcerating secondary syphilis showed lower CD4 counts (9 patients, CD4 = 307, SD 140/μl).

Serology (table 3) Eighty one of 151 patients (54%) showed inappropriate serological response to syphilis infection. Inappropriate was defined as strongly reactive VDRL (⩾ 512) or TPHA (⩾ 10240) titres, false negative IgM or IgG tests or other serological findings, inconsistent with the patients' clinical features.

In detail serum VDRL (see table 3) was not reactive in 2 patients with secondary syphilis, in 2 patients with neurosyphilis and in 5 patients with latent syphilis (and positive IgM-titres or extremely high TPHA titres). Two patients with primary syphilis had nonreactive VDRL tests but positive dark-field examinations. Eight of 130 patients (6·2%) showed VDRL titres ⩾ 512. In one patient with maculopapular syphilides TPHA and VDRL were not reactive. The diagnostic criteria in this special case were a characteristic exanthema, plasma cell infiltrates in the histological examination and a typical Herxheimer reaction after the initiation of penicillin treatment.

TPHA showed strongly reactive titres (⩾ 10 240) in 47 of 141 (33·3%) patients. 19S-IgM-FTA-ABS-tests were not reactive in 16 of 103 patients (15·5%), including 3 patients with primary syphilis, 5 patients with secondary, 6 patients with neurosyphilis and 2 patients with latent syphilis (see table 3). Among the 47 patients with extremely high TPHA titres the 19S-IgM-FTA-ABS-test was false non reactive in 5 (10·6%) patients and not performed in 12 (25·5%) cases. In patients with neurosyphilis (25) the 19S-IgM-FTA-ABS-test was nonreactive in 6 cases (24%). Among these 6 patients 3 (50%) had strongly reactive TPHA-titres (⩾ 10 240).

Only in 28 of 151 patients were SPHA tests performed. They were not reactive in 7 of 28 (25%) cases with clinical or serological active syphilis.

Therapy Syphilis therapy was not standardised in this retrospective analysis. For unknown reasons two patients did not receive any treatment. Because of confirmed or presumed penicillin allergy 15 of 149 (10·1%) patients were not treated with penicillin or derivates. They received erythromycin (n = 6), doxycyclin (n = 5), ceftriaxone (n = 2), cefotaxime (n = 1) or rolitetracyclin (n = 1) treatment. Only 6 of the remaining 134 (4·5%) patients treated with penicillin received benzathine penicillin. Among all 149 patients treated in this study, treatment failure was reported in 6 cases

Table 3 Syphilis serology in 151 HIV+ patients

	VDRL (130¶/151)					*TPHA (141¶/151)*					*19S IgM-FTA-ABS (103¶/151)*			*Total patients*
	*	†	‡	§	*nd*	*	†	‡	§	*nd*	*	‡	*nd*	
Primary syphilis	2	6	10	0	8	0	2	16	5	3	3	18	5	26
Secondary syphilis syphilides	2	3	33	1	5	1	1	24	14	4	5	21	18	44
Secondary syphilis ulcerating	0	1	6	2	2	0	0	5	5	1	0	8	3	11
Neuro-syphilis	2	5	13	2	3	0	2	13	9	1	6	14	5	25
Latent syphilis seropositive	5	7	22	1	3	0	5	21	12	0	2	20	16	38
Others	2	0	3	2	0	0	2	2	2	1	0	6	1	7
Patients	13	22	87	8	21	1	12	81	47	10	16	87	48	151

* = Not reactive.
† = weak reactive (i.e. VDRL ⩽ 8, TPHA ⩽ 160).
‡ = reactive (i.e. VDRL = 16–256, TPHA 320–5120).
§ = strongly reactive (that is, VDRL ⩾ 512, TPHA ⩾ 10 240).
nd = not done.
¶ serology results available.

(4·03%). Two patients with penicillin, 2 patients with clemizole penicillin as well as 1 patient with erythromycin treatment did not respond to therapy. The treatment of the sixth patient, reported as a treatment failure, is unknown. No detailed information was given about therapy controls in most of the 151 cases evaluated for this retrospective study. Many of the syphilis patients had not returned for subsequent care.

Discussion

In the decade 1982–1992 the total incidence of syphilis registered in West Germany decreased from 8 to 1·4 cases per 100 000 inhabitants per year (Statistisches Bundesamt; personal communication). In the same period an extremely high seroprevalence rate for syphilis (26 to 58%) was found in HIV infected patients in Germany.[4–6] In accordance with these results, we detected 151 cases of active syphilis among 11 368 HIV positive patients (1, 33%). Based on our data the estimated odds of syphilis in HIV-infected patients are 17 times higher than in the general population.

Almost all clinical features of syphilis in HIV-infected patients reported in the literature[14] were found in our patients. Furthermore syphilis patients were found in all stages of HIV disease (table 1). The small number of syphilis patients in stage CDC I is a consequence of the small number of early stage HIV disease monitored at our clinics. As shown in tables 1 and 2 early syphilis is diagnosed in patients with an early stage of HIV infection, whereas ulcerating secondary syphilis and neurosyphilis are more prevalent in patients with advanced immunodeficiency.

For clinical and prognostic reasons ulcerating secondary syphilis with general symptoms (in Europe often classified as "malignant syphilis") and neurosyphilis are of special importance in the immunocompromised host. Immunological deficiencies seem to intensify the ability of *Treponema pallidum* to invade the central nervous system.[9 10 15] This is the reason for an increased frequency of neurosyphilis in HIV infected patients, its unusual severity and reduced responsiveness to treatment. In the pre-AIDS era neurosyphilis was diagnosed as a lifetime event in approximately 10% of all patients with untreated syphilis. The latency period was stated to be 7 to 30 years.[16] We now demonstrate that the odds of neurosyphilis in HIV infected patients with syphilis is nearly twice as high as in syphilis patients in the general population. Moreover, neurosyphilis is more likely to occur in advanced stages of immunodeficiency (table 1). In general, the manifestation of neurosyphilis is expected in late secondary and tertiary syphilis. Already in 1924 Chesney[17] detected *Treponema pallidum* in CSF during the early stage of syphilis. In the setting of immunodeficiency caused by HIV this might be a frequent event and the period of latency until the manifestation of clinical symptoms might be very short.[18] In several cases neurological symptoms were already detected in early syphilis.[10] We conclude from our study that cerebrospinal fluid analysis for syphilis serology (VDRL/TPHA reactivity), concentration of protein, and cell counts should be performed in any HIV infected patient with syphilis, even if neurological symptoms (visual or hearing complaints, history of headache, dizziness) are mild or absent. Neurosyphilis is difficult to diagnose without evidence from lumbar CSF. It is necessary to exclude other HIV-associated CNS diseases like toxoplasmosis, cryptococcosis or HIV dementia. Therefore 5 patients who had been reported to have neurosyphilis by different GASG clinics were withdrawn from further evaluation in the neurosyphilis group. Their diagnosis was based on clinical symptoms and reactive syphilis serology (in the serum) only. These 5 patients had questionable CSF findings or they had refused lumbar puncture. To clarify unclear cases of neurosyphilis routine CSF analysis should be completed by detection of treponemal DNA by PCR methods.[19]

Ulcerating secondary syphilis with general symptoms (in Europe often diagnosed as "malignant syphilis") is characterised by rupia-like ulcerating skin lesions and general symptoms like severe fever, weakness etc. In this study ulcerating secondary syphilis was found in 7·3% of all syphilis patients, which is about 60 times more frequent than in a historical control group.[20]

The reason for the high frequency of ulcerating secondary syphilis could be the consequence of immunodeficiency. This hypothesis is suggested by the low mean CD4 cell count found in this group of syphilis patients. It seems that the cellular immune functions in an immunocompetent host protect against severe and ulcerating skin lesions. Consequently, rupia-like skin lesions which are an almost pathognomonic sign of this type of secondary syphilis should be recognised by physicians taking care of HIV-infected patients.

The interpretation of the various serological phenomenona, observed in our retrospective multicentre study, is complicated by the fact that diagnostic methods had not been standardised. There is a controversy about the influence of HIV infection on conventional and new diagnostic tests for syphilis diagnosis.[21] Therefore in 1994 GASG initiated a prospective syphilis study using a reference laboratory, standardised documentation, and standardised treatment for all participating clinics.

Owing to the late onset of cardiolipin antibody production (about 5 weeks after infection) non reactive VDRL tests can be expected in early primary syphilis. Some of the non reactive VDRL tests observed in undiluted specimens of patients with clinical symptoms of secondary syphilis might be the result of the prozone phenomenon: An excess of non-treponemal antibodies, presumably produced by HIV induced B-cell dysfunction, prevents the antibody-antigen reaction in standard tests. Such false-negative standard tests seem to be more frequent in HIV-positive patients com-

pared with the general population.[22 23]

In two patients with an exanthema suspected to be secondary syphilis the diagnosis was confirmed by typical clinical signs: a non itching maculopapular exanthema involving palms and plants, and a histology showing infiltrates of plasma cells. In both patients an immediate response to penicillin treatment was observed. One patient with a negative VDRL had a positive TPHA and a positive 19S-IgM-FTA-ABS-test. In the other patient VDRL and TPHA were both negative. The diagnostic criteria for active secondary syphilis in this case were a characteristic maculopapular exanthema, plasma cell infiltrates in the histological section and a typical Herxheimer reaction after the initiation of penicillin treatment. A Warthin-Starry-silver stain was not performed.

False non reactive results in the highly sensitive specific 19S-IgM-FTA-ABS-test are possible in patients with very high specific IgG antibody titres and in late syphilis. One third (47 patients) of the patients investigated in our study had such high IgG titres (TPHA $\geqslant$ 10 240). This could explain why 16 of 103 (15·5%) patients tested for 19S-IgM-FTA-ABS had false non reactive results.

Among the 47 patients with very high TPHA titres 5 (10·6%) had false non reactive 19S-IgM-FTA-ABS-tests. Considering that the 19S-IgM-FTA-ABS-test was not performed in 12 of these 47 patients, the percentage of false non reactive 19S-IgM-FTA-ABS-tests might be markedly higher.

In HIV-negative patients the 19S-IgM-FTA-ABS-tests showed a very high sensitivity in early syphilis (82–100%) and secondary syphilis (70–100%). In late syphilis a markedly poorer sensitivity was found (60–79%) by the same authors.[24 25 26] According to these findings our patients with neurosyphilis and a non reactive 19S-IgM-FTA-ABS-test (6/25) had reactive (3 patients) or strongly reactive ($\geqslant$ 10 240) TPHA-titres (3 patients). Influences by previous exposures to antibiotics and a general decrease in the strength of antibody response with increased duration of infection[27] may be responsible for false negative results in late disease. In cases of reinfection the 19S-IgM-FTA-ABS-test showed a sensitivity of 87%.[24]

As reported by other authors[9 10] relapses of syphilis with early manifestation of tertiary syphilis and meningovascular neurosyphilis have to be expected in immunocompromised patients, especially after "one shot" treatment with benzathine penicillin. Obviously benzathine penicillin does not reach effective CSF levels against *Treponema pallidum*. As one shot therapy for syphilis is uncommon in Germany only 6 of 149 (3·9%) patients received benzathine penicillin (3 × 2·4 million IU, weekly intervals). We did not see any treatment failures to benzathine penicillin in these 6 patients.

Six treatment failures (persistent lesions, none or less than fourfold drop in titres) were reported under treatment with other derivatives of penicillin and erythromycin. The reasons for these treatment failures are unknown but reinfections or reactivation of persisting treponema might be discussed. Even high doses of penicillin recommended for neurosyphilis are not consistently effective.[28] Therefore clinical and serological follow-up is absolutely important in all HIV-infected syphilis patients.

Retrospective chart reviews are of limited value in many aspects. However, this study was designed to obtain information about the frequency as well as clinical and serological features of active syphilis in patients with coexistent HIV infection. In contrast to the epidemiological data in HIV-infected intravenous drug users with syphilis, reported by Gourevitch *et al*,[29] we found a remarkably high number of atypical clinical and serological courses in our study population (78·8% homosexual or bisexual men). We conclude that all HIV-infected patients should be tested for syphilis, irrespective of being infected by homosexual or heterosexual contacts or by intravenous drug abuse. In cases with incompatible serological and clinical findings additional diagnostic procedures like histology or PCR of treponemal DNA should be performed.

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Cobblestones The seed of an ulcer

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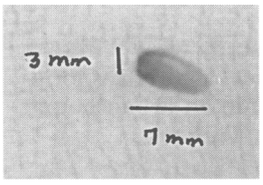

Necrotic vegetable seed measuring 7 × 3 mm.

A 34 year old Caucasian heterosexual male, a civil servant, presented to the clinic with a penile ulcer, which he noticed on the day of attendance. Neither he nor his regular partner had had any oral or genital ulceration before. He had not applied any topical treatment to the penis nor inserted a foreign body. Examination revealed a preputial ulcer with an underlying hard nodule measuring 7 × 3 × 1 mm which was squeezed out easily (fig). Microscopy showed that it was necrotic vegetable material, possibly a seed.

Implantation of foreign bodies under the skin of the penis to enhance coital excitement and orgasm of the sexual partner during intercourse has been reported. This practice appears to be quite common in Thailand, where it is performed by unqualified people in prisons and among lower socio-economic groups. The procedure entails piercing the penile skin with a sharp instrument without local anaesthetic, and inserting one or more beads in to the superficial fascia. Most beads are derived from the bottoms of pomade glass jars, but other objects such as stones, bullets, grains of rice, pearls, and jewels may also be used.[1] The resulting artificial penile nodules are diagnosable by the stony hardness of the implanted beads. Foreign body implantation can be complicated by incarceration, granulomatous reaction, abscess formation, fistula or ulcer as in our case.

Unlike the previously reported cases of foreign body implantation our patient seems to have acquired the seed unwittingly, possibly through oro-genital contact.

1 Lim KB, Seow CS, Tulip T, Daniel M, Vijaysingham SM. Artificial penile nodules: case reports. *Genitourin Med* 1986;**62**:123–5.